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ROENTGENOLOGIC AND SCINTIGRAPHIC

METHODS FOR EXAMINATION

OF THE PARASTERNAL LYMPHATICS

Experimental and clinical studies using different contrast

media and technetium-99m sulfide colloid

Lund 1973

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by

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- I. GÖRANSON L.R. , JONSSON K. & OLIN T.: Transabdominal roentgenologic and scintigraphic lymphography of the ventral mediastinum with Thorotrast and $^{99}\text{Tc}^{\text{m}}$ -S colloid in the rabbit.
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- V. GÖRANSON L.R. & JONSSON K.: Parasternal scintigraphy with technetium-99m sulfide colloid in humans. A comparison between two techniques.
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Reference to these papers will be made by the numerals I - V.

CONTENTS

	Page
INTRODUCTION	7
A. TRANSABDOMINAL TECHNIQUE	10
MATERIAL AND METHODS	10
RESULTS	12
DISCUSSION	13
CONCLUSIONS	15
B. THE SUBCUTANEOUS TECHNIQUE	15
MATERIAL AND METHODS	16
RESULTS	17
DISCUSSION	18
CONCLUSIONS	20
GENERAL SUMMARY AND CONCLUSIONS	21
REFERENCES	22



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INTRODUCTION

Mastectomy in patients with carcinoma of the breast usually includes an exeresis of the axilla, excising all palpable lymph nodes. HULTBORN et coll (1955) demonstrated by a radioactive tracer technique that all parts of the breast drain both to the parasternal and to the axillary lymph nodes. Only certain groups of surgeons, for instance ANDREASSEN et coll (1954) and URBAN & MARJANI (1971), have performed an exploration of the parasternal lymph nodes in connection with mastectomy. The results of these two groups demonstrate the clinical importance of the parasternal lymph nodes in carcinoma of the breast: ANDREASSEN et coll (1954) found metastases in these lymph nodes in one third of medially and in one tenth of laterally located carcinomas and URBAN & MARJANI (1971) in 33 per cent of an entire group of 725 patients. The latter authors found parasternal lymph node metastases alone without involvement of other lymph nodes in 8 per cent of their patients.

Techniques for correct preoperative diagnosis of tumour involvement of the parasternal lymphatics have until now been limited. The lymph nodes are not accessible for direct palpation as they are located on both sides of the sternum along the internal mammary arteries and veins (Fig. 1), but various diagnostic methods have been described. HANDLEY & THACKRAY (1949, 1954) have presented a method for biopsy of these lymph nodes but, despite the very good results obtained, the method does not seem to be in common use. MASSOUD et coll (1964) have reported a series with tomography of the ventral mediastinum, in most cases with induced pneumomediastinum. KETT et coll (1970) have described a method for direct lym-

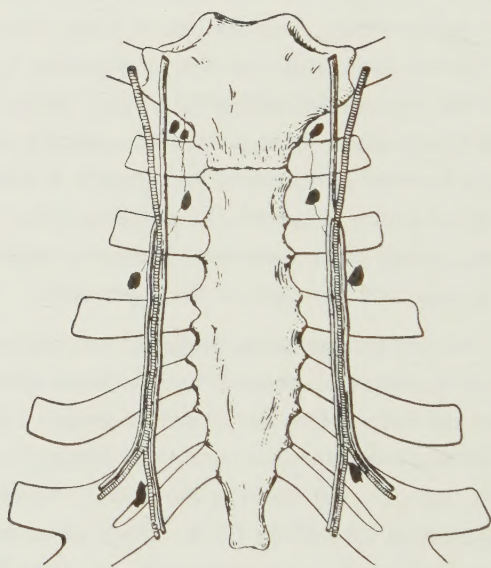


Fig. 1. The parasternal lymphatics. From STIBBE (1918).
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phography of lymph vessels in the breast, but it seems to be of limited value for demonstration of the parasternal lymphatics. Transsternal phlebography may also be used for the detection of parasternal lymph node metastases, but reliable results are obtained only for nodes in the first and second intercostal spaces (CHERNOMOR-DIKOVA et coll 1972).

Scintigraphy is the most common diagnostic tool for demonstrating the parasternal lymph nodes. ¹⁹⁸Au colloid has thus far been the most commonly used indicator. The radioactive tracer substance has been injected subcutaneously/intracutaneously on both sides of the xiphoid process, or dorsal to the process in the midline, whence it is absorbed by the lymphatics draining to parasternal lymph vessels and nodes.

There is also another way to demonstrate the parasternal lymphatics. The lymphatics of the diaphragm absorb particles, macroparticles and blood corpuscles from the peritoneal cavity, and drain to the parasternal lymph vessels. There are several roentgenologic reports, demonstrating this route of absorption using Thorotrast or iodized oil emulsions injected into the peritoneal cavity (transabdominal technique).

The objective of the present investigation was to demonstrate the parasternal lymphatics by the two principally different techniques: A. the transabdominal one, using different contrast media and a radioactive tracer substance, and B. the subcutaneous one, using a radioactive tracer technique.

A. TRANSABDOMINAL TECHNIQUE (papers I, III and V)

The lymphatic absorption from the peritoneal cavity has been the object of great interest for more than 100 years. A roentgenologic method for demonstrating the parasternal lymphatics, using Thorotrast, was first described by HELD (1932) and by MENVILLE & ANÉ (1932). The contrast medium was absorbed and filled the parasternal lymph vessels and cranial mediastinal lymph nodes. These findings have been confirmed in rats (HELD 1932, OLIN & SALDEEN 1964, LINDGREN et coll 1968) and rabbits (MENVILLE & ANÉ 1932, POMERANZ 1934, EFSKIND 1941). OLIN & SALDEEN (1964) also demonstrated contrast filling of paravertebral and mediastinal lymph vessels, and of retroperitoneal and ileocecal lymph vessels and nodes in rats.

The same intraperitoneal injection technique has been used in the study of the absorption of iodized oil emulsions (BENNETT & SHIVAS 1953/54, KOEHLER 1965, DUMONT et coll 1967, KOEHLER & RODRIGUEZ 1968, ELKE 1972) and enabled demonstration of the parasternal lymphatics. ATKINS et coll (1970) have shown in an human subject that $^{99}\text{Tc}^{\text{m}}$ -S colloid, injected into the peritoneal cavity, is absorbed and accumulated in lymph nodes of the mediastinum.

MATERIAL AND METHODS

The transabdominal technique was studied in experimental animals using Thorotrast (paper I), iodized oil emulsions (paper III) and $^{99}\text{Tc}^{\text{m}}$ -S colloid (paper I), with special reference to the injection site of the contrast medium or the radioactive tracer substance. The transabdominal technique was then applied in a clinical group of 9 patients with carcinoma of the breast (paper V), using $^{99}\text{Tc}^{\text{m}}$ -S colloid, prepared according to PERSSON & NAVERSTEN (1970).

Thorotrast was injected into the peritoneal cavity of 16 rabbits (paper I) either selectively below the diaphragm, using a thin catheter, or non-selectively in the caudal part of the abdomen. The influence of hyaluronidase (Hyalas, Leo, Sweden) and polyphlorethin phosphate on the absorption was tested.

$^{99}\text{Tc}^{\text{m}}$ -S colloid was injected selectively below the diaphragm, or non-selectively in the peritoneal cavity in 15 rabbits (paper I), and the uptake in the parasternal lymphatics was recorded on a gamma-camera (Nuclear Chicago, Pho/Gamma III). The influence of hyaluronidase and polyphlorethin phosphate was also tested.

Guerbet Laboratories (France) have developed two new contrast media, both of which are iodized oil emulsions. One of them (AG 60-99) is stable, and the particles of the emulsion are 1 μm or less in size. The other contrast medium (AG 52-315) has to be shaken with two parts of 5.5 per cent glucose before use and, when shaken by hand, the particles of the emulsion are around 15 μm in size. The two contrast media were injected into the peritoneal cavity of rabbits, rats and guinea-pigs. AG 60-99 was injected both non-selectively and selectively below one hemidiaphragm in rabbits.

The clinical application of the animal experiments consisted of an investigation in which 9 patients with carcinoma of the breast were studied by intraperitoneal injection of $^{99}\text{Tc}^{\text{m}}$ -S colloid (paper V). The tip of the needle for injection of the colloid was checked by fluoroscopy to be in the free peritoneal cavity. The uptake of the radioactive tracer substance in the parasternal lymph nodes was followed by a gamma-camera (Nuclear Chicago, Pho/Gamma III).

RESULTS

All of the contrast media tested were absorbed by the diaphragmatic lymphatics in rabbits, draining to the parasternal lymph vessels and lymph nodes in the cranial part of the mediastinum. The fine particle emulsion (AG 60-99) was also noted in the thoracic duct.

Thorotrast and AG 52-315 demonstrated the same pattern of absorption: the contrast media were first noted in lymph nodes in the upper ventral part of the mediastinum. The concentration of the contrast media in the lymph nodes increased as the absorption continued. When Thorotrast was used, filling of the parasternal lymph vessels starting at the nodes and proceeding caudally, was later observed. The absorption of Thorotrast was slightly enhanced by hyaluronidase, and was retarded by polyphlorethin phosphate.

AG 60-99 was absorbed almost immediately, and could be detected in the parasternal lymph vessels within 2 to 5 minutes. It was possible to make a unilateral "selective" study of the parasternal lymph vessels, provided that the contrast medium was injected selectively below either hemidiaphragm, and that the injection was made slowly, with a small amount of contrast medium. A local inflammatory reaction in the peritoneal cavity was, however, seen after this contrast medium.

No absorption of the two iodized oil emulsions was noted in rats and guinea-pigs.

The study of $^{99}\text{Tc}^{\text{m}}$ -S colloid in rabbits demonstrated a rapid uptake of the radioactive tracer substance in the cranial mediastinal lymph nodes when a selective injection was made, and a somewhat slower absorption when using the non-selective technique. Hyaluronidase and polyphloreitin phosphate had no influence on the absorption of the technetium colloid.

No parasternal lymph nodes were found in rabbits either with contrast media or with technetium-colloid. In humans, parasternal lymph nodes could be identified in 3 patients out of 9, following the injection of technetium-colloid into the peritoneal cavity. Bilateral lymph nodes were noted in two patients, while the third had unilateral uptake of the colloid. In the remaining 6 patients, a diffuse uptake of the tracer substance was noted in the mediastinum, and no parasternal lymph nodes could be identified.

DISCUSSION

Demonstration of the parasternal lymphatics in experimental animals following injection of Thorotrast into the peritoneal cavity is well known. Use of this contrast medium in humans is no longer permitted because of its radioactivity and its affinity for the reticulo-endothelial system, which can be injurious. When the fine-particle oil emulsion (AG 60-99) was used in rabbits, filling of the parasternal lymph vessels in the experimental animals was observed almost immediately (paper III). It is not advisable, however, to use this contrast medium in humans, as an inflammatory reaction was seen in the vicinity of the contrast medium remaining in the peritoneal cavity.

In the search for a medium that could be used in man, technetium colloid was suggested for scintigraphy. It proved to be excellent in rabbits (paper I), demonstrating the same lymph nodes as were seen roentgenologically when Thorotrast was used. No parasternal lymph nodes could be demonstrated in rabbits, either with the contrast medium or with the radioactive tracer substance: only the bilateral groups of lymph nodes in the cranial part of the mediastinum were seen. It is not clear whether the parasternal lymph nodes are lacking in rabbits or are simply too small to be clearly seen. The experimental investigations (paper I) demonstrated that the $^{99}\text{Tc}^{\text{m}}$ -S colloid was readily absorbed to the lymphatics without the addition of hyaluronidase. ATKINS et coll (1970) have shown in one human subject that the technetium-sulfur colloid is similarly absorbed, and this finding has been confirmed by our clinical investigation. Previous abdominal surgery might have some influence upon absorption, and also increases the risk for unsuccessful injection into the free peritoneal cavity.

It was found that the transabdominal technique had several disadvantages:

1. The injection must be performed under fluoroscopy, making the appropriate equipment necessary for the procedure,
2. The colloid was easily trapped at the site of injection, presumably by the omentum,
3. Most patients examined with this technique were elderly, which prevented manipulation of the patient to enhance the absorption (prone and head-down positions).

CONCLUSIONS

It is possible to make a roentgenologic examination of the parasternal lymphatics in animals with a transabdominal technique, but the available contrast media cannot be used in humans because of secondary effects. $^{99}\text{Tc}^{\text{m}}$ -S colloid can be used for parasternal scintigraphy in animals as well as in humans, using a transabdominal technique. The technique has, however, several disadvantages which limit its usefulness.

B. THE SUBCUTANEOUS TECHNIQUE (papers II, IV and V).

The lymphatic drainage of the cranial part of the abdomen and the chest wall, including the breast, is maintained through the parasternal lymph vessels (ROUVIERE 1932). This fact has been utilized in previously published reports on parasternal lymph scintigraphy. In most reports ^{198}Au colloid has been used, injected on both sides of the xiphoid process or dorsal to the process in the midline (SCHENK 1966, SCHENK et coll 1966, ROSSI & FERRI 1966, DIETHELM et coll 1966, ROSSI et coll 1968, MICHAÏLOV et coll 1968, KAZEM et coll 1968, 1969, MEYER-BURG & WILHELMI 1971, SEIFERT & BETZNER 1970, GROS et coll 1969, 1972).

It has been shown (HAUSER et coll 1969, HERTING et coll 1970) that the local radiation dose (absorbed dose in rads) is very high when ^{198}Au is used for scintigraphy, and radiation necrosis of the skin has been reported (HAAS et coll 1970). The physical properties of technetium are much more favourable than those of ^{198}Au : there is no beta-radiation, and the half-life is only 6 hours, so the local radiation dose is much lower.

MATERIAL AND METHODS

The subcutaneous technique was tested in experimental animals to see if $^{99}\text{Tc}^{\text{m}}$ -S colloid, injected subcutaneously on both sides of the xiphoid process, could be used for parasternal scintigraphy (paper II) and to ascertain how external factors affect the scintigraphy (paper IV). Its clinical application was assessed in patients with carcinoma of the breast (paper V).

Rabbits were examined (paper II) after injection of the colloid subcutaneously/intracutaneously on both sides of the xiphoid process. In the first group no pharmacological agent was added to the colloid. The injection of technetium-colloid in the second group was preceded by the injection of hyaluronidase (Hyalas, Leo, Sweden) subcutaneously/intracutaneously, two minutes before the colloid on each side of the process. The third group was injected with colloid mixed with hyaluronidase thereby ensuring that the hyaluronidase and the colloid were injected at exactly the same site.

External factors that might affect the scintigraphy with $^{99}\text{Tc}^{\text{m}}$ -S colloid were investigated in rabbits (paper IV). The following factors were tested:

1. Repeated examination (one week, and one month or more after the first examination);
2. Incision of the chest wall and excision of subcutaneous tissues with or without resultant postoperative infection;
3. Intraperitoneal injection of different contrast media; and
4. Intraperitoneal injection of rabbit blood.

Parasternal lymph vessels and cranial mediastinal lymph nodes were dissected in animals injected with Thorotrast and rabbit blood, and examined histologically.

The subcutaneous technique was used in 10 patients with carcinoma of the breast, to test the clinical usefulness of the method.

Indirect lymphography with subcutaneous injection of AG 60-99 (paper III) in the interdigital web or in the soft tissues on either side of or on both sides of the xiphoid process in rabbits was tested, both with and without the addition of hyaluronidase.

RESULTS

The only method demonstrating a constant bilateral uptake of radioactive tracer substance in the lymph nodes of the experimental animals was that in which the hyaluronidase was dissolved in the colloid (paper II). The reliable method was then used in all of the remaining investigations (papers IV and V).

Consecutive studies had no effect on each other (paper IV). The incision and excision of subcutaneous tissues of the chest wall resulted in post-operative wound infection in 9 of 12 animals, but affected the parasternal scintigraphy negatively in only one. This animal had a widespread inflammatory reaction in the wound, and the ipsilateral lymph nodes failed to fill with tracer substance. In 4 cases with wound infection, the uptake of the tracer substance in the ipsilateral group of mediastinal lymph nodes was greater than was usually seen, which might indicate a hypertrophy on that side.

The injection of an iodized oil emulsion (AG 60-99) in the peritoneal cavity of rabbits did not impair the lymph scintigraphy. The intraperitoneal injection of Thorotrast and heparinized blood caused blockage of the parasternal lymph flow in two animals and one animal, respectively. Histologic examination of the cranial-ventral mediastinal lymph nodes showed the presence of blood and Thorotrast in the nodes. Thorotrast caused an inflammatory reaction in the lymph nodes, resulting in obstruction of the sinusoids. Secondary to this, as an obstruction phenomenon, the parasternal lymph vessels were dilated and distended with the contrast medium. The iodized oil emulsion was minimally absorbed, when injected subcutaneously.

In the clinical material, uptake of the radioactive colloid was noted in parasternal lymph nodes of 7 of the 10 patients. In 5 cases it was bilateral and in 2 cases unilateral. In one patient, uptake was registered in a lymph node of the medial pectoral group.

DISCUSSION

It was shown in paper II that the only reliable technique for parasternal scintigraphy with $^{99}\text{Tc}^{\text{m}}$ -S colloid in experimental animals was that in which hyaluronidase was dissolved in the colloid. When the hyaluronidase was given before the colloid the two solutions were not necessarily injected in the same layer of the cutis.

It has been claimed (RÖSLER 1971) that post-operative scintigraphy after mastectomy is of limited value, because the detritus and the inflammatory reaction in the wound causes blockage in the parasternal lymph vessels, making the scintigraphy less reliable.

The investigation does not permit of the conclusion that a mastectomy has no effect on the scintigraphy, but a biopsy of the breast should not affect the scintigraphy, as a biopsy is performed under fully sterile conditions.

COURTICE et coll (1953) and HAHN et coll (1944) have demonstrated that blood injected into the peritoneal cavity is absorbed via the parasternal lymph vessels. This was confirmed in the present investigation (paper IV) and it was shown by scintigraphy that the intraperitoneal blood may block the flow of lymph. This indicates that intraperitoneal bleeding, for instance after an abdominal operation, or intraperitoneal tumour cells might block the parasternal lymph flow and influence the scintigraphic examination. Thorotrast caused a definite blocking for the scintigraphy in two cases, which was proved by histology.

The clinical investigation (paper V) has shown that the subcutaneous technique is superior to the transabdominal one for scintigraphy of the parasternal lymph nodes in humans. It has two technical advantages:

1. no equipment for fluoroscopy is needed; and
2. the position of the patient does not affect the examination.

The main problem, however, is the interpretation of the scintigrams. The normal anatomical variations of the parasternal lymph nodes are considerable, with respect to both number and position (STIBBE 1918). These variations have been demonstrated with parasternal scintigraphy in normal patients by MEYER-BURG & WILHELM (1971). As the resolution in lymph scintigraphy is poor, details of the single lymph nodes are not discernible. The only scintigraphic way of detecting

lymph node metastases is by demonstrating blockage of the lymph flow. It has been claimed that the failure of a lymph node chain to fill is proof of metastasis. In our clinical material (transabdominal and subcutaneous examination techniques) there are 3 patients with unilateral uptake to the parasternal lymph nodes. In these cases, the carcinoma was ipsilateral to the non-filled side, which might indicate blockage due to metastasis. MEYER-BURG & WILHELMI (1971) have, however, demonstrated normal patients with no uptake to the lymph nodes. Another type of scintigram which is difficult to interpret correctly is that in which tracer substance has been taken up by a lymph node in the fourth or fifth intercostal space, but in no node cranial to that position (paper V, Fig. 1 a). It is not clear whether this type represents blockage of the cranial part due to metastasis. The uptake of tracer substance in cranial parasternal lymph nodes on the other hand indicate a proper lymph flow (paper V, Fig. 2). The difficulties encountered at interpretation indicate that great need for an investigation with an exact correlation between parasternal scintigraphy and operative findings in the parasternal lymph nodes at, for instance, an extended radical mastectomy, as described by URBAN & MARJANI (1971).

CONCLUSIONS

$^{99}\text{Tc}^{\text{m}}$ -S colloid, mixed with hyaluronidase, is well fitted for use in parasternal scintigraphy with subcutaneous technique. Minor surgical trauma to the thoracic wall or breast should not affect the scintigram. In the experimental animal the injection of Thorotrast and blood into the peritoneal cavity may affect the scintigraphy.

GENERAL SUMMARY AND CONCLUSIONS

No roentgenologic technique for examination of the parasternal lymphatics in humans is available as yet^{x/}, but the present investigation has shown that they can be examined scintigraphically with a subcutaneous technique, as well as with a transabdominal one, using $^{99}\text{Tc}^{\text{m}}$ -S colloid. In most previously published investigations ^{198}Au colloid has been used for parasternal scintigraphy, but technetium colloid is preferable due to its favourable physical properties. The subcutaneous technique is preferable to the transabdominal one, because it requires less technical equipment, involves a smaller risk of complications and is not influenced by the position of the patient.

The clinical aim of the present investigation has been to detect parasternal metastases from carcinoma of the breast. The only scintigraphic way to detect metastases is to demonstrate blockage of the lymph flow. If cranial lymph nodes are filled with the radioactive tracer substance, this ought to indicate a proper lymph flow with no metastases.

The wide anatomical variations make interpretation of the scintigram difficult. This difficulty stresses the need for further investigation, where findings at parasternal scintigraphy are compared to and correlated with operative findings.

x/ After the articles had been accepted for publication, a report by MEYER-BURG (1973) appeared, describing a method for direct lymphography of the parasternal lymphatics: a lymph vessel on the surface of the liver is cannulated during laparoscopy, and contrast medium injected, which drains to parasternal lymphatics.

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